Institution: University of Cambridge		
Unit of Assessment: 2		
Title of case study: Reducing breast and ovarian cancer occurrences in women at high risk		
Period when the underpinning research was undertaken: 2001-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Antonis Antoniou	Professor of Cancer Risk Prediction	2001 to present
Douglas Easton	Professor of Genetic Epidemiology	1995 to present
Paul Pharoah	Professor of Cancer Epidemiology	1999 to present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Breast and ovarian cancers are leading causes of death and disability globally. BOADICEA – a powerful, user-friendly, web-based prediction tool – identifies women at especially high risk of cancer, empowering their decisions about potentially life-altering preventive actions such as pre-emptive surgical removal of breasts or ovaries. Endorsed for use by NICE, the American Cancer Society and other major national and international bodies, BOADICEA is used thousands of times daily in 91 countries, supporting women, doctors, and genetic counsellors. Across the world, BOADICEA supports hundreds of thousands of women in making decisions each year, contributing towards lower cancer incidence and mortality, improved quality of life and reduced costs.

2. Underpinning research (indicative maximum 500 words)

Breast cancer is the most common cancer among women, with more than 2,000,000 new cases each year globally. In the UK, it kills over 11,000 women every year. Ovarian cancer, the gynaecological cancer with the poorest survival rate, affects 300,000 women around the world annually, and kills over 4,000 women in the UK each year (World Cancer Research Fund and Cancer Research UK statistics).

A dilemma for many women – whether to take life-altering pre-emptive action to stop the development of cancer

Some women are at especially high risk of developing breast or ovarian cancer because of their genetic profile and other risk factors. They may have to make decisions about whether to take high-consequence preventive actions. One such action involves surgical removal of breasts or ovaries and fallopian tubes before any disease is apparent. Another possible pre-emptive strategy involves chemoprevention, which requires long-term daily use of hormone drugs (e.g. tamoxifen). Although these interventions are effective, they are risky, costly and potentially life-altering, and the decisions about them are hard to make.

A tool to empower personalised decisions

Cambridge University-led research has produced a user-friendly, web-based prediction tool to inform and empower women and their healthcare professionals to make these decisions. Known for short as BOADICEA (after the British warrior-queen), the "Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm" has been co-produced with patients, doctors, genetic counsellors, cancer charities and other end-users, and has involved researchers from many disciplines over more than 15 years. The initial version of BOADICEA was launched in 2008, and it has been continuously improved since then.

Identifying new predictors of cancer

The tool's model incorporates information on multiple genetic and other risk factors identified through advances in molecular epidemiology. Cambridge University-led research has identified more than 200 common genetic alterations that are associated with breast and ovarian cancers [1,2], and developed novel "polygenic risk scores" that can summarise information on many such genetic variants across the genome [3]. Cambridge has also led the analytical work that identified several novel breast and ovarian cancer susceptibility genes, including *PALB2*,

CHEK2 and *RAD51D* [4] and established the most precise cancer risks for rare genetic alterations in these and other known risk genes [5–7].

Cambridge University research underpinning BOADICEA includes the development of novel statistical techniques for modelling susceptibility to cancer [5], and early adoption of new "chip" technology that can survey the genome to identify new risk factors for cancer [1]. These developments generated powerful new data in Cambridge-led cohorts of cancer patients and healthy individuals, and allowed pooling of data from studies around the world in international consortia led by Cambridge researchers. The consortia include the Breast Cancer Association Consortium (more than 300,000 breast cancer patients and controls contributed by 110 research groups worldwide) and the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (more than 80,000 patients/carriers contributed by research teams globally).

Improving the tool and facilitating wide access to it

Applying novel statistical techniques developed by Cambridge to the data from these large consortia has allowed estimation of cancer risks for genetically susceptible individuals, and identified genetic factors strongly associated with raised risk. These discoveries [1–7] have been rapidly incorporated into BOADICEA, making the prediction tool increasingly accurate. The genetic discoveries have also been shown to lead to cost-effective risk-stratified screening programmes [8]. BOADICEA has been independently validated by researchers outside Cambridge, and has been shown to perform well in different countries and circumstances.

Since 2014, the prediction tool has incorporated many additional genetic risk factors, as well as behavioural, hormonal, reproductive risk factors, clinical and imaging risk factors [9]. In January 2020, the team further enhanced the accessibility of the BOADICEA algorithm by releasing CanRisk (www.canrisk.org). This web tool incorporates the latest version of the BOADICEA algorithm, and uses an up-to-date and user-friendly web interface.

3. References to the research (indicative maximum of six references)

1. **Easton D,** Pooley KA, Dunning AM, **Pharoah P**, Thompson D, Ballinger DG, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 2007; 447: 1087–1093. doi:10.1038/nature05887*
2. Michailidou K., Lindström S, Dennis J, Beesley J, Hui S, …, **Easton D.** Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017; 551:92–94. doi:10.1038/nature24284*
3. Mavaddat N, Michailidou K, Dennis, Lush M, Fachal L, …, **Easton D**. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2019 104(1): 21-34. doi:10.1016/j.ajhg.2018.11.002*
4. Rahman N, Seal S, Thompson D, Kelly P, …, **Easton D**, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007; 39:165–167. doi:10.1038/ng1959*
5. **Antoniou A,** Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; 371:497-506. doi:10.1056/NEJMoa1400382*
6. Kuchenbaecker KB, Hopper JL, Barnes DR, …, **Easton D**, **Antoniou A**, and the BRCA1 and BRCA2 Cohort Consortium. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* 2017; 317 (23):2402-2416. doi:10.1001/jama.2017.7112*
7. **Easton D**, **Pharoah P**, **Antoniou A**, Tischkowitz M, Sean V. Tavtigian SV, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015; 372:2243-2257. doi:10.1056/NEJMsr1501341*
8. Pashayan N, Morris S, Fiona J. Gilbert FJ, **Pharoah P**. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. *JAMA Oncol* 2018; 4(11):1504-1510. doi:10.1001/jamaoncol.2018.1901*
9. Lee A., Mavaddat N, Wilcox AN, Cunningham AP, …, **Pharoah P**, **Easton D**, **Antoniou A**. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genetics in Medicine* 2019; 21: 1708–1718. doi:10.1038/s41436-018-0406-9*

*These publications have been peer reviewed, providing evidence of research quality.

Examples of competitive funding received

Cancer Research UK (CRUK), Programme Grant (C12292/A20861 PI: Antoniou; co-Is: Easton, Pharoah): "Development of risk prediction models…" 1/5/2016 (5 years), GBP1,996,719
CRUK, Senior Cancer Research Fellowship (C12292/A11174, PI Antoniou; co-I: Pharoah): "Development of risk prediction algorithms…" 1/10/2009 (6 years), GBP1,242,441
European Commission, H-2020 (EU 634935-BRIDGES, PI: Easton & Devilee; co-I: Antoniou): "Breast cancer risk after diagnostic gene sequencing" 1/9/2015 (5 years), EUR6,200,000
CRUK Programme Grant (C1287/A16563 : PI: Easton, co-I: Antoniou) "Genetic Epidemiology of Cancer" 1/10/2013 (5 years), GBP1,700,000
European Commission, FP7 (HEALTH-F2-2009-223175; PI: Per Hall, Scientific Director: Easton) "Collaborative Oncological Gene-Environment Study" 1/5/2009 (5 years) EUR16,700,000

4. Details of the impact (indicative maximum 750 words)

Improving health outcomes for women through precise cancer risk prediction

Given the major risks and costs of potentially life-altering preventive actions in relation to breast and ovarian cancer, patients and healthcare professionals need access to robust, personalised and powerful risk prediction estimates to help make good decisions. Before development of the BOADICEA prediction tool, women at high risk could be identified only by their family history of cancer or by testing for genetic alterations in a few genes (notably *BRCA1/2*). Those methods were too crude to enable women to make well-informed decisions about whether to take – or not to take – highly consequential actions such as pre-emptive surgical treatment or chemoprevention.

A multidimensional approach to personalised risk assessment

The Cambridge-led BOADICEA tool is distinguished by its ability to calculate personalised estimates of women's future risks of developing breast or ovarian cancer. Incorporating multiple different types of complementary information, it spans the full spectrum of genetic risk factors from high-impact rare variants to modest but common variants. The tool also calculates the likelihood of carrying mutations in the moderate to high-risk genes (including *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2*).

Importantly, BOADICEA incorporates information on key non-genetic factors, including behavioural influences, hormonal risk factors, and mammographic density. The tool assigns appropriate weights to these predictors to generate individualised risk calculations that inform and empower women to make personalised decisions about high-stakes preventive action. By improving the effective and efficient targeting of interventions, supporting genetic counselling, and enabling women to make decisions based on evidence personalised to them, BOADICEA has helped reduce mortality, reduce distress, and avoided unnecessary procedures and costs.

Impact on national and international guidelines

The value of the BOADICEA tool is recognised by policy-makers and cancer organisations globally. In 2017, the US National Comprehensive Cancer Network, an alliance of 30 leading cancer centres in the United States, endorsed the use of BOADICEA in its guidelines [A]. In 2015, the American Cancer Society, a leading organisation dedicated to eliminating cancer, recommended use of BOADICEA [A]. So too have the Ontario Breast Screening Programme (representing Canada's most populous province) and Australia's eviQ clinical guideline [A].

First adopted by National Institute for Health and Care Excellence (NICE) in 2006, BOADICEA is also now recommended by the UK Cancer Genetics Group, the NHS Breast Screening Programme and regional NHS genetic counselling programmes [B,C]. It is one of only two breast cancer risk assessment tools recommended by the latest NICE guidelines (published in 2017) and NHS Breast Screening Programme guidelines (2020) [B].

Widespread global use

BOADICEA is available free of charge to healthcare professionals everywhere. Since its international launch in 2008, BOADICEA has attracted more than 16,700 registered users from over 70 countries worldwide [D]. Worldwide usage grew substantially following updated releases of the tool in 2014, when BOADICEA was customised for multiple countries including the USA, Canada, Australia and European countries. By 2018, over 250,000 risk calculations were carried out using BOADICEA in a single year [D].

In November 2019, BOADICEA became the first cancer risk prediction tool to gain approval as a medical device (CE marking) from the UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA) [D]. The current version of the web tool, released in January 2020 on the CanRisk website (https://canrisk.org/about/), incorporates the latest version of the BOADICEA algorithm and uses an up-to-date and user-friendly web interface to enable rapid and easy risk calculations. By November 2020, only ten months after release, over 3,800 healthcare professionals from 91 countries had registered on CanRisk, using BOADICEA to make more than 133,000 new risk calculations [D]. Risk-scoring systems based on Cambridge's research are also used by commercial software and genetic test providers [E].

Empowering women

BOADICEA has empowered thousands of women at high risk of cancer to make more informed decisions about disease prevention, including relatives of women who have had breast or ovarian cancer and women with relevant gene mutations. BOADICEA predictions are also widely used by patient-oriented support groups, including the FORCE Cancer Charity in the United States, which states that Cambridge's research has *"been critical for developing our resources for people with mutations in these genes, for guiding critical decisions on planning their cancer screening, the timing of risk-reducing mastectomy and risk-reducing oophorectomy for the early detection and prevention of breast and ovarian cancer. These are allowing us to provide an enhanced experience to women at hereditary risk of breast and ovarian cancer"* [F].

Impact on clinical practice

Healthcare professionals in the UK and beyond use predictions obtained by BOADICEA to provide a consistent way of deciding whether to refer individuals for *BRCA1* and *BRCA2* mutation screening and whether to refer women for enhanced breast cancer screening (e.g. annual mammography from a younger age, or with MRI). This focuses healthcare resources on women most likely to benefit [C], avoiding unnecessary anxiety for those at lower risk and enabling those at higher risk to make prevention and screening decisions sooner.

Another important impact is in improving the use of gene panel tests. Around 12,000 of these tests, which analyse multiple genes at once and incorporate several genes and risk estimates identified by the Cambridge team [G], are done each year in the UK. But, if targeted at the wrong groups, gene panel tests (like screening) can lead to unnecessary worry and cost. BOADICEA is now routinely used by clinical genetics services and breast screening programmes worldwide to triage women for enhanced screening and gene panel tests [A–C]. Polygenic risk scores developed by the team have also formed the basis for two large ongoing breast cancer screening trials in Europe (MyPeBS, n=85,000) and the USA (Wisdom, n=100,000) [H].

Clinical geneticists, genetic counsellors, oncologists, GPs and others use BOADICEA to support them in shared decision-making with patients. Cancer risk estimates for high- and moderate-risk genes developed by the Cambridge team have been incorporated into genetic counselling and breast cancer screening protocols in the UK, US, Netherlands, Australia, New Zealand and other countries [A–C,I].

In the UK, the British Society for Genetic Medicine's Cancer Genetics Group, a national organisation covering clinicians, counsellors and scientists with expertise in hereditary predisposition to cancer, states that risk estimates provided by BOADICEA are *"integral to routine practice in clinical cancer genetics"* and *"essential in the everyday clinical practice in guiding and informing critical decisions for women with pathogenic variants in these genes"*

[C]. In Canada, risk assessments using BOADICEA are routinely undertaken for patients referred to familial breast and ovarian cancer clinics [I]. BOADICEA has been incorporated into other decision support tools for cancer prevention decision-making (e.g. iPREVENT [D]).

Impact on health outcomes

BOADICEA algorithms have contributed significantly towards early detection and prevention of cancer. For example, between September 2015 and January 2019, 2,033 women in Cambridge received detailed genetic testing guided by BOADICEA risk predictions. Around 10% of these women had serious mutations putting them at high risk of breast or ovarian cancer. All women with serious mutations received MRI scans to identify early stage breast cancers and were offered preventive intervention (removal of ovaries and fallopian tubes or breast) [J]. As another example, between March 2015 and December 2018, 1,052 women in Bristol received detailed genetic testing guided by BOADICEA predictions [J].

A reasonable extrapolation of estimates from Cambridge to other settings where BOADICEA is in widespread use suggests that this tool – when coupled with appropriate pre-emptive action – is contributing to significant reductions in cancer mortality. Prophylactic removal of the ovaries and fallopian tubes cuts the risk of ovarian cancer occurrence by more than 90% (*Cochrane Database of Systematic Reviews* 2018), while prophylactic removal of breasts cuts the risk of breast cancer occurrence by at least 80% (*NEJM* 1999). Under the assumption of 52,800 risk calculations undertaken in the UK each year (around a fifth of all tests using BOADICEA are carried out in the UK [D]), genetic testing guided by BOADICEA risk predictions helps avoid around 120 deaths from ovarian cancer and 60 deaths from breast cancer annually [J]. Scaled to the worldwide use of BOADICEA, the tool's personalised risk calculations are thus contributing to more appropriate interventions and better health outcomes for thousands of women.

5. Sources to corroborate the impact (indicative maximum of ten references)

A. **(i)** Ontario Breast Cancer Screening Programme p. 1; **(ii)** eviQ Australian clinical management guidelines. pp. 1-2; **(iii)** *Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening* p. 35; **(iv)** NCCN Clinical Practice Guidelines in Oncology 2017: *Genetic/Familial High-Risk Assessment: Breast and Ovarian* pp. 4, 51 ; **(v)** NCCN Guidelines v.1.2021, pp. 4–5, 40.
B. **(i)** NICE Guidance CG164, *Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer* (2013; updated in 2017 and 2019) pp. 7, 26; **(ii)** PHE Guidance: *Protocols for surveillance of women at very high risk of developing breast cancer* (updated 23 September 2020), p. 6
C. UK Cancer Genetics Group testimonial.
D. **(i)** BOADICEA web tool and log of use; **(ii)** CanRisk web tool and log of use; **(iii)** iPREVENT implementation of BOADICEA.
E. **(i)** FamHis tool: https://famhis.net/products/; **(ii)** Myriad Genetics; PHENOTIPS (https://phenotips.com); **(iii)** Myriad myRisk: https://myriadmyrisk.com/riskscore/; **(iv)** AmbryScore-breast: www.ambrygen.com/clinician/ambryscore/breast; **(v)** Brevagen: www.brevagenplus.com; **(vi)** Genomics PLC: www.genomicsplc.com/precision-health/.
F. Testimonial from FORCE Cancer Charity
G. Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. pp. 3–4, 6
H. **(i)** MyPeBS: https://mypebs.eu/; **(ii)** Wisdom: https://www.thewisdomstudy.org/
I. **(i)** Breast Screen Australia monitoring report 2018. Screening guidelines for Australia and New Zealand p. 2; **(ii)** eviQ guidelines "BRCA1 or BRCA2 – risk management (female)" p. 1; **(iii)** eviQ guidelines: BRCA1 and BRCA2 genetic testing pp. 1, 2, 4, 6 **(iv)** Australian Government, Recommendations on Genetic Testing for women diagnosed with ovarian cancer. pp. 2, 5; **(iv)** Testimonial from Canada Clinical Genetics Programme
J. **(i)** Data submitted to PHE on BRCA testing by clinical diagnostics laboratories in England, 2019; **(ii)** Correspondence regarding diagnostic yield and intervention rates; **(iii)** Modelling data and calculations